1029-18 Promotion of Collateral Growth (Arteriogenesis) by Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) in Patients With Coronary Artery Disease

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Experimentally, activated macrophages have been documented to induce vascular proliferation.

Methods: In 21 patients (pts; 11 men, age 74±9years) with three- vessel coronary artery disease eligible for PTCA of ≥1 stenotic lesion, the effect of GM-CSF on quantitatively assessed collateral flow was tested in a randomized, double-blind, placebo-controlled fashion. The study protocol consisted of an invasive baseline and follow-up collateral flow index (CFI, no unit) measurement immediately before intracoronary (ic) injection of 40µg of GM-CSF (n=10) or placebo (n=11), and after a 2-week treatment period with subcutaneous GM-CSF (10µg/kg) or placebo, respectively. CFI was determined by simultaneous measurements of mean aortic (P_{ao}, mmHg), coronary wedge (P_{occl}, mmHg) and central venous pressure (CVP, mmHg):

$CFI=(P_{occl}-CVP)/(P_{ao}-CVP)$.

Results: see table. *: p<0.05

Conclusions: This first clinical study investigating the potential of GM-CSF to improve collateral flow in patients with coronary artery disease documents its efficacy in a short-term administration protocol. It remains to be determined whether promotion of collateral growth by GM-CSF sustains during long-term follow-up, and whether alternative routes of administration are more effective.

Results

	GM-CSF	Placebo	P
LV ejection fraction at baseline (%)	65±10	58±18	NS
Leucocytes after treatment (109/l)	14.5±6.7	7.5±3.6	0.01
Ic ECG ST segment during PTCA after treatment normalized	4/10	0/11	0.01
CFI before treatment	0.21±0.14*	0.30±0.16	NS
CFI after treatment	0.32±0.24*	0.23±0.11	NS
Delta CFI after-before treatment	+0.11	-0.07	0.01

1029-19 Therapeutic Angiogenesis via Selective Retroinfusion of FGF-2 and VEGF Into the Femoral Vein in the Chronic Ischemic Hindlimb

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With the aim to enhance therapeutic angiogenesis by increasing tissue binding of angiogenic growth-factors, selective retroinfusion of the femoral vein was performed in the chronically ischemic rabbit hindlimb. In separate scintigrafic experiments, tissue concentration of Tc-99m-Nano-colloids in the ischemic hindlimb was 4-fold increased following retroinfusion compared with antegrade delivery.

Hindlimb ischemia was induced through excision of the femoral artery in 15 male rabbits (day 0). 7 days postoperatively selective retroinfusion into the femoral vein of the ischemic hindlimb was performed during complete stop of arterial blood flow over 30 min: [bFGF-group] with bFGF protein (50µg), [FGF2+VEGF-group] with a combination of FGF2 (50µg) and VEGF Protein (20 µg) or with saline [controls].

Results:

1. collateral growth between day 7 (= baseline) and day 35 (angiography) was higher in both treated groups compared with controls (*= p<0.05)
2. capillary density (alcaline phosphatase staining) was higher in both treated groups
3. blood flow (cine frame count validated by doppler flow measurement) increased between day 7 (= baseline) and day 35 in both treated groups.

Conclusion: Selective retroinfusion of FGF2 and/or VEGF protein into the femoral vein induced effective therapeutic angiogenesis (collateral and capillary growth), leading to higher blood flow to the ischemic hindlimb. There was a consistent trend towards a more effective angiogenesis following retroinfusion of FGF2+VEGF.

	control	bFGF Retroinfusion	bFGF+VEGF Retroinfusion
Collateral growth	12.9±3.6	61.0±29.0*	83.0 ±8.0*
Capillary density	0.9±0.2	1.6±0.1*	1.7±0.1*
Blood flow	9±13	43±3*	44±8*

1029-20 High Pressure, Retrograde, Coronary Venous Delivery of FGF-2 Protein Improves Coronary Blood Flow in a Porcine Model of Myocardial Ischemia

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Background: Effective delivery of angiogenic factors to ischemic myocardium remains a practical challenge. We compared delivery of FGF-2 protein via high pressure, retrograde injection into the anterior interventricular vein (AIV) with intracoronary (IC) administration in a porcine model of chronic myocardial ischemia.

Methods: Copper stents were deployed in the left anterior descending (LAD) coronary arteries of 17 pigs, resulting in gradual occlusion of the vessel and chronic myocardial ischemia. At 4 weeks, myocardial blood flow at rest and during pacing was measured in all pigs using fluorescent microspheres. In 8 pigs, FGF-2 protein (6 mcg/kg) was delivered via retrograde injection into the AIV at a pressure of 100 mmHg. Six pigs received a similar total amount of FGF-2 by IC delivery into the three major coronary arteries, and 3 pigs served as controls. Four weeks later, myocardial blood flow was reassessed. Post sacrifice, the hearts were divided into 48 segments, and myocardial flow in each segment was analyzed for microsphere evidence of ischemia prior to and 4 weeks after treatment. Ischemia was defined as a greater than 10% decrease in blood flow during pacing. The average absolute flow, during pacing, in the LAD region before and after treatment was also calculated for each arm.

Results: There were fewer ischemic segments (a decrease in ischemic burden) after treatment in 50% (4/8) of the AIV pigs, versus 17% (1/6) of the IC pigs, and 0% (0/3) of the control pigs. The percentage of ischemic myocardial segments *decreased* by an average of 4% per pig in the AIV arm, compared to an *increase* of 23% in the IC arm and 28% in the control arm (p<0.001, AIV compared to IC or control). Average flow (ml/min/gm tissue) in the LAD region during pacing increased significantly from pre-treatment to after treatment in the AIV arm by 22% (0.73 to 0.93, p<0.0001), did not change significantly in the IC arm (1.1 to 1.0, p=0.6), and decreased significantly by 20% in the control arm (1.4 to 1.1, p=0.04).

Conclusion: Delivery of FGF-2 protein via high pressure, retrograde injection into the AIV may represent a practical and effective means for improving chronic myocardial ischemia.

1029-21 Acute and Long-Term Safety of Pressurized Myocardial Transvenous Delivery: Confirmation by Biochemical, Echocardiographic, and Histologic Parameters

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Background: Advances in cardiovascular gene, stem cell and growth factor therapy necessitate effective local delivery methods to the heart. This study evaluated the immediate and long-term (28-day) safety of regional myocardial drug delivery by pressurized myocardial transvenous injection. **Methods**: In 8 anesthetized swine, a balloon-tipped catheter cannulated the anterior interventricular vein (AIV) via the internal jugular vein and coronary sinus. During balloon occlusion a pressurized injection of saline (10 ml at an internal venous pressure of 100 mmHg) was made into the AIV. Cardiac markers were measured and echocardiograms were recorded at baseline, 30 minutes, 4 hours and 28 days post-injection. Histologic analysis was performed at 4 hours or 28 days (n=4 for each). **Results**: There was no echocardiographic evidence of regional wall motion abnormality in the acute or chronic phase post-injection and limited cardiac marker release (Table). Histologic studies showed limited early disruption but no significant myocardial necrosis. **Conclusions**: Regional pressurized myocardial transvenous delivery is safe and well tolerated in the porcine model. The findings support a potential role for protein, cell or gene delivery in patients.

Baseline		30 minutes		4 hours	
CKMB mass (ng/ml)	Troponin T (ng/ml)	CKMB mass	Troponin T	CKMB mass	Troponin T
<0.10	<0.01	<0.10	0.01		
<0.10	<0.01	<0.10	0.09		
0.13	<0.01	0.13	<0.01		
0.18	<0.01	0.14	<0.01		
<0.10	<0.01			<0.10	0.12
<0.10	<0.01			<0.10	<0.01
0.18	<0.01			<0.10	<0.01
<0.10	<0.01			<0.10	<0.01

Normal ranges: CKMB mass <5.0 ng/ml; Troponin T <0.01 ng/ml